Coronary artery high take-off in rodents and the possible involvement of Smad2

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The coronary arteries (CAs) supply the mammalian heart with oxygenated blood. They arise from the right and left aortic valve sinuses at the aortic root. In humans, the occurrence of a CA arising ectopically from the tubular aorta, a condition called high take-off (HTO), is rare (<0.4%) and predisposes to sudden cardiac death. We have shown that HTO is relatively frequent in some laboratory mouse strains, and preliminary studies suggests that the Smad2$^{rs29725537:C>A}$ (Smad2$^{C>A}$) allele is associated with HTO in this species. In order to test whether HTO occurs in association with Smad2$^{C>A}$ in other rodents, we examined the anatomical origin of the CAs, by means of stereomicroscopy and a corrosion cast technique, in 3,388 specimens belonging to 17 rodent species. In addition, Smad2 DNA sequence from *M. musculus* was compared by Blastn analyses with that from six of the species examined in which this sequence is known (*Mus spretus*, *Rattus norvegicus*, *Apodemus sylvaticus*, *Myodes glareolus*, *Mesocricetus auratus*, *Microtus agrestis*). HTO occurred in nine out of 17 species studied. The incidence of HTO ranged from 0.4% to 6.5% (low) in three species and from 15.9% to 25% (high) in six species. The Smad2 sequence showed similarities higher than 75% for the whole gene, and higher than 71% for the intron sequence that includes the rs29725537:C>A Single Nucleotide Polymorphism. The Smad2$^{C>A}$ allele was identified only in *M. spretus* and *A. sylvaticus*, with high incidences of HTO, whereas *R. norvegicus*, *M. glareolus*, *M. auratus* and *M. agrestis* showed low or null incidences. We conclude that HTO is a common trait in rodents, which does not lead to cardiac pathology probably due to the intramyocardial condition of their CAs, as opposed to the human subepicardial CAs. The Smad2$^{C>A}$ allele may be involved in the development of HTO and probably other phenotypes in different rodent species.

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